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14. **ABSTRACT**
All active, potentially curative treatments for clinically localized prostate cancer damage quality of life. Brachytherapy,or radioactive seed implants, theoretically may increase the target radiation dose and thus improve control of cancer. has been rapidly adopted in the U.S. despite limited long-term published outcomes, in part because of its convenience apparently attractive toxicity profile. However, our recent survey of brachytherapy patients after longer follow-up surprisingly frequent urinary incontinence and erectile dysfunction. Retrospective evidence suggests that reducing theradiation dose to the urethra may prevent later urinary incontinence. A recent refinement of conventionalbrachytherapy technique targets only the peripheral zone of the prostate, sharply reducing the dose to the urethra, andattempts to reduce radiation "cold spots" by using intraoperative feedback from real-time magnetic resonance imaging(MRI). Using our validated cancer-specific scales, our pilot data suggested that the altered brachytherapy technique hadthe intended benefit but also unexpected outcomes. We have extended our cohort study of 276 brachytherapy patientsand now compare 3- and 24-month outcomes of this technique to standard ultrasounded-guided brachytherapy.

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BACKGROUND

Prostate cancer is a unique malignancy because of the uncertain but probably modest efficacy of available local treatments for early (non-metastatic) cancer, the potential for long-lasting treatment-related urinary, bowel and sexual function problems, its unusually long typical natural history. As a result the great majority of patients experience any permanent symptoms for more than a decade, and its great impact on the American population, the highest incidence and second highest prevalence of any non-cutaneous malignancy in the United States (1). The most recent estimate is over 1.8 million men. Nearly one million had survived 5 years and a quarter million 10 years or more. Most men are diagnosed with early (non-metastatic) cancer, for which local therapy may be curative, but because of the prostate's anatomical location may lead to sexual, urinary and bowel dysfunction (2-6). The great majority of these men will be treated with either external beam radiation therapy (XRT), radical prostatectomy (RP), or ultrasound guided interstitial prostate radiation therapy (BT), also known as brachytherapy or seed implants. BT is now widely available, despite still sparse efficacy data (7, 8). Complication rates of the alternative local treatments differ qualitatively and quantitatively. All active treatments for prostate cancer produce erectile dysfunction (ED) in most men, and long-term urinary incontinence (after RP and brachytherapy) and bowel dysfunction (after EBRT) are common (3, 5, 6, 9-14).

Although early experience with brachytherapy using freehand placement of radioactive seeds in open pelvic surgery yielded both unsatisfactory control of cancer and high post-treatment complication rates (15-18), a percutaneous ultrasound-guided technique developed by Blasko, Ragde and colleagues in Seattle dramatically improved three-dimensional radiation dose distributions (13-15). As a result, brachytherapy was reevaluated (7), resulting in its now wide availability in the United States (19). Randomized comparisons between modalities are rare and flawed, although a randomized trial of RP vs. initial observation has recently found evidence of a small benefit for surgery (20, 21) at a cost in quality of life (22). Retrospective, prognostically-stratified comparisons of RP to XRT have appeared (23, 24), and more recently one between ultrasound-guided brachytherapy and RP or XRT (8). Based on a multivariable time to PSA failure analysis of patients stratified by previously-defined pretreatment risk groups, low risk patients ($T_{1c,\ 2a}$ and PSA ≤ 10 and Gleason ≤ 6) had comparable PSA failure free survival at 5 years after RP, XRT, or brachytherapy, but brachytherapy patients at high (T_{2c} or PSA > 20 or Gleason ≥ 8) or intermediate risk (T_{2b} or Gleason 7 or PSA > 10 and ≤ 20) had significantly worse cancer control than patients managed with RP or XRT.

BT, like other prostate cancer treatments, affects patient quality of life. Our team documented one of the most important complications, the risk of long-term urinary incontinence. Although acute urethral irritation and urinary obstruction are well-documented short-term complications of standard ultrasound-guided BT (27-33), reports by treating physicians after relatively short follow-up (median 18-45 months) indicates little evidence of long-term complications (27-29, 31, 34). However, because of the potentially long delay after brachytherapy for some symptoms, especially urinary incontinence and erectile dysfunction (ED), and the usually greater complication rates obtained directly from patients rather than treating physicians, in part because of patients' reluctance to complain to their doctors (2, 5, 6,

11, 35), we felt these reports may underreport long-term complications of BT, especially urinary incontinence and erectile dysfunction. However, there is some evidence that the bowel problems associated with external beam radiation therapy (EBRT) are less frequent in BT.

To better define long-term BT-associated side effects, we performed a cross sectional survey of the earliest large patient cohort treated by the Seattle group completed at a median of 5 years after treatment. We found that 38% of BT patients who had not had comorbid procedures like transurethral resection of the prostate (TURP) reported some degree of urinary incontinence. These results may be partly explained by the older age of the patients in that early cohort (median: 75 years) and by preexisting pretreatment dysfunction our cross-sectional survey could not document. However, the outcome is consistent with the phenomenon of acute urethral necrosis the Seattle physician group had previously described (36), and the prevalence of urinary incontinence we found is much higher than expected in men in that age group. Subsequent retrospective studies supported the belief that the primary risk factor producing long-term incontinence is the proportion of the urethra receiving high-dose radiation (31, 37). Reduced radiation to the urethra was subsequently associated with reduced incontinence (38). The MBT technique addresses this problem by excluding the periurethral transition zone of the prostate from the target volume for radiation, trading the risk of allowing cancer in the transition zone to persist after treatment in exchange for decreased urethral irradiation in the hope that late urinary incontinence will also be decreased. Because cancers in the transition zone are much less frequent than those in the peripheral zone and may have a more indolent course, this technical change may benefit patients overall, although the benefit and harms require empirical verification. This project follows on a recently completed project, Outcomes of Alternative Brachytherapy Techniques for Early Prostate Cancer (DAMD17-02-1-0090), to determine whether a quality of life benefit can be demonstrated in the first 2 years after BT. The current project continues that project for an additional 3 years. Unfortunately, the first project was delayed by 10 months for DAMD IRB review of the project, which had previously been approved by all participating institutions' own IRBs. Therefore, follow-up is delayed by that amount. We present interim results from the new study, which closely overlap the results we presented in the Final Report of the earlier project.

METHODS

Patient Population

Patients are recruited from 4 Boston-area treatment programs directed by three outstanding brachytherapy experts: Brigham and Women's Hospital, directed by Dr. Anthony D'Amico, the Massachusetts General Hospital, directed by Dr. Anthony Zietman, and Beth Israel –Deaconess and MetroWest Hospitals, both directed by Dr. Irving Kaplan. The first 3 sites are in Boston and the fourth in Framingham, MA. Before treatment, investigators or study staff at the Massachusetts General Hospital Center for Outcomes Research give or send all eligible patients the baseline study instrument, along with a cover letter describing the study from the Principal Investigator and their treating physician. The few patients who do not respond within two weeks are contacted by telephone. Enrolled patients are registered with the Quality Assurance Office for Clinical Trials (QAOCT) at the Dana Farber Cancer Institute by study staff.

At each specified follow-up interval from initiation of therapy, 3, 12, and 24 months, we mail patients a cover letter and follow-up questionnaires containing the same instruments as the pretreatment baseline questionnaire, along with postage paid return envelopes. Data are collected by the staff of the Center for Outcomes Research at Massachusetts General Hospital. Using an in-house relational database system, study participants are assigned a unique study identification number used to track the patients until follow-up is complete or the patient drops out of the study. Automated follow-up procedures flag when participants should receive a postcard, follow-up mailing, or telephone call. Weekly statistical reports detail the status of respondents. Data management is performed at QAOCT, the data management center for all studies of the Dana Farber/Partners Cancer Care. The QAOCT data manager confirm eligibility, register patients and ensure that study parameters are followed.

Data Collection

Patients are asked to complete self-administered questionnaires that include assessments of sexual function, urinary and bowel complications of treatment, and disease-focused quality of life we previously validated (39, 40). An experienced genitourinary oncology research nurse abstracts information from medical records regarding demographic characteristics, cancer prognostic factors, comorbid diseases, treatments and subsequent clinical course using the forms developed in earlier studies.

Data Analysis

We report treatment groups by baseline symptoms and sociodemographic characteristics using Fisher's exact test for categorical measures and Wilcoxon rank-sum tests for continuous measures. Effect sizes (ES) are calculated by dividing mean score difference by the standard deviation at baseline.

RESULTS

As of January 27, 2006, the project has recruited a total of 276 patients, including 201 in the two ultrasound-guided "conventional" brachytherapy treatment groups ($USBT_1$ and $USBT_2$) and 75 in the MRI-guided treatment group (MBT). Each patient completed the baseline questionnaire (See Appendix, Baseline Questionnaire) before treatment. Follow-up questionnaires have been received as follows: 228 1-Month Questionnaires (86% of the 265 enrolled and eligible patients now at least 1 month after treatment, including 16 patients who dropped out of the study before the first follow-up questionnaire), 224 3-Month Questionnaires (86% of 265 patients 3 months out, with 24 total dropouts), 185 12-Month Questionnaires (84% of 221 patients 12 months out, with 26 total dropouts), and 108 24-Month Questionnaires (66% of 161 patients 24 months out, with 27 total dropouts). The retention in the study has been excellent, with only 4 patients dropping out after 3-month follow-up, although additional 40 patients have not yet returned their most recent questionnaire, of whom 24, including 20 who were sent the 24-month questionnaire, received them more than 1 month ago and may drop out of the study. However, we are hopeful that most of those will be returned, since only 2 of 189 patients dropped out between 3- and 12-month follow-up questionnaires. We report the results of the most recent analysis, as of November 25, 2005.

Pretreatment characteristics. The enrolled patients include 75 patients who received the experimental MRI-guided technique (MRBT) and 201 patients receiving conventional ultrasound-guided brachytherapy (SBT), 116 patients treated by one physician ($USBT_1$) and 85 patients treated by another ($USBT_2$) (Table 1). The entire group was predominantly Caucasian and socioeconomically advantaged. More than three-fourths were currently married at study enrollment and had attended at least some college, and 30% had attended at least some graduate school. Patients enrolled in the study were close to the median age at diagnosis for prostate cancer patients, currently 68 years, and older than many current surgical cohorts, especially those reported from referral centers, which attract patients younger, healthier and more mobile compared to those treated in community facilities.

Clinical prognostic factors, for both prostate cancer and other comorbid medical diseases, were also on average favorable for the study population. The median pre-treatment PSA for all groups was 5 ng/ml, fewer than 1 in 5 patients had Gleason scores greater than 6, more than 90% were non-palpable clinical Stage 1 tumors, and more than three-fourths fell into the D'Amico low risk group. Patients had slight comorbid disease burdens, measured by the Index of Co-Existent Disease (ICED). Nearly one-third had no other medical diagnosis, and nearly all the remaining patients had diagnoses that were asymptomatic (ICED 1). However, the MBT patients had still more favorable demographic characteristic compared to USBT patients, suggesting that their more robust pretreatment function may represent less vulnerability to treatment-related dysfunction. They were younger (median: 64 years vs. 68 years for USBT patients; P= 0.002) and better educated (10% high school or less and 54% graduate school vs. 23% and 29%, respectively; P= 0.0002). However, patients undergoing different treatment techniques had no significant differences in tumor parameters, including pretreatment PSA, Gleason score, clinical stage and D'Amico risk group, nor other indicators of health status, including ICED score and both Physical and Mental Component Summaries of the SF-12. In summary, patient pretreatment characteristics indicate greater self-selection for MBT by patients with both younger age, a global indicator of medical comorbidity, which increases with age in the study population's age range (49 to 81 years of age), and the most important predictor of social position, educational attainment. Further, trends in many pretreatment variables favored MBT patients. However, statistical significance was not achieved for tumor characteristics or any other preclinical parameters, and, other than modestly younger age in the $USBT_2$ group (median 67 vs. 69 years for $USBT_1$ patients; P= 0.02), the two USBT treatment groups appear similar in all other characteristics.

Functional Outcomes. Because of occasional omitted responses, baseline scores could be calculated for 267 of the 276 enrolled patients. Study patients had little reported urinary incontinence or bowel problems before treatment. However, urinary obstruction/irritation was evident, and patients reported even more sexual dysfunction (Table 2). Patient groups did not differ significantly in any measured category of dysfunction, either between the MBT and USBT groups or between USBT subgroups. The trend favoring the MBT group did not achieve significance because of the great variability among patients (SD for USBT and MBT 29.5 and 21.9, respectively), but suggested possible lesser vulnerability by MBT patients to treatment-related dysfunction.

However, our study documented increased dysfunction for all scales after treatment. The time frame for the timing and magnitude of changes differed by symptom group. We do not report the 1-month and 12-month results. Although we surveyed patients 1 month after treatment to ensure that symptoms did not decline between 1 and 3 months after treatment, the 1-month scores differed little from the 3-month scores. The 12-month results were in each case intermediate between 3- and 12-month results. While analyses when this cohort is more mature may reveal unique aspects of patients at the 12-month interval, we omit them here in order to concentrate on the more important contours of our cohort's outcomes.

Urinary and bowel dysfunction were greatest for all groups at 3 months after treatment, while sexual dysfunction increased markedly between 3 and 24 months, consistent with our prior observations and those of others that sexual dysfunction continues to increase for at least 36 months after radiation treatments. However, we also found differences in the outcomes between groups receiving different brachytherapy techniques. Surprisingly, we found differences not only between the MBT and USBT groups, but also between the USBT treatment groups.

Urinary dysfunction. By both measures of urinary dysfunction, the MBT treatment group had smaller increases in urinary symptoms than the combined USBT group or either subgroup, providing evidence that the technique's primary toxicity reduction goal was at least partially successful. The results were most evident for the most feared acute complication of brachytherapy, urinary obstruction/irritation. At 3 months after treatment, both groups reported mean scale increases approaching or greater than the 10-point change in these 0-100 scales generally acknowledged to represent clinically significant changes. However, USBT patients' mean increase was more than double that of the MBT patients (23.8 vs. 9.3), and the more symptomatic group, $USBT_{2,}$ was 3-fold higher than the MBT group (29.4). By 24 months, as we anticipated, these symptoms had markedly attenuated, as had the differences between USBT subgroups, but the mean difference for the USBT patients remained 8.4 higher than before treatment, suggesting persisting dysfunction surpassing the 10-point clinical significance standard for at lest some patients. In contrast, the mean score for MBT patients was virtually unchanged at 24 months compared to the pretreatment baseline.

The pattern was similar but attenuated for urinary incontinence, which overlaps somewhat with urinary obstruction/irritation. The MBT patients' mean change was 2.6 on the urinary incontinence scale at 3-month follow-up, approximately half the 10-point change generally acknowledged to be clinically significant, and even that small change was erased by 24 months after treatment. The average increase in the USBT group was 3-fold higher at 8.7 points, approaching the 10-point standard of clinical significance. However, the Hospital 2 USBT subgroup ($USBT_2$) had more than twice the Urinary Incontinence scale increase compared to the Hospital 1 subgroup ($USBT_1$). The different between USBT subgroups was markedly attenuated by the 24-month follow-up.

Bowel problems. In our prior comparison of short-term (3-month) changes, using smaller, non-contemporaneous patient groups from our earlier cohort study, we found that MBT patients had greater increases in bowel problems (42). Our current results provide little support for the earlier observation, although the nominal increase from pretreatment baseline to both the 3- and 12-month follow-up is greater than for the combined USBT group. However, again differences

are apparent between USBT subgroups, although smaller than for the urinary dysfunction scales. At each follow-up interval, the more symptomatic group, $USBT_2$, reported a mean increase greater than the MBT group, nearly erasing the modest difference between the MBT group and the $USBT_1$ subgroup.

Sexual Dysfunction. As noted above, sexual dysfunction was prevalent in the entire study population. However, the MBT and USBT patients differed before treatment, as did the USBT subgroups. The mean difference of 12.1 favoring the MBT group over the USBT group was larger than the 10-point clinical significance standard, as was the 11.2 point mean difference between $USBT_1$ and $USBT_2$ favoring the latter patients. The increases in sexual dysfunction progressed over time, as the modest overall mean increase of 2.8 patients by 3 months after treatment increased to 10.2 at 24 months. In contrast our earlier observation that MBT patients had lesser increases in sexual dysfunction, the current MBT cohort reported nominally greater mean increases in dysfunction than the combined USBT group. However, although results were identical at 3 months after treatment, when little sexual dysfunction had appeared, here again different results by USBT subgroup could be observed by 24 months, when significant dysfunction had become apparent. While dysfunction increased in the $USBT_1$ subgroup by less than that of the MBT patients (5.2 vs. 12.6), the $USBT_2$ group reported a mean increase in dysfunction nominally greater than the MBT patients.

CONCLUSIONS

Our study, as yet immature, adds substantial new information to the question of whether modifying brachytherapy technique can result in improved functional outcomes by reducing treatment-related toxicity. Although longer follow-up is necessary before rendering definitive conclusions about the outcomes of our study groups, our results provide gratifying confirmatory evidence that the MBT technique, which sharply reduces radiation to the periurethral transition zone of the prostate, produces the intended reduction in short-term urinary symptoms of a probably clinically significant magnitude, at least for some patients, measured by both urinary incontinence and urinary obstruction/irritation scales. These results are consistent with our earlier observation, made in a less satisfactory study population (42). While reassuring and indicating potential relief from the threat of worsened short-term symptoms of urinary obstruction/irritation and presumably decreased risk of potentially very painful complete urinary obstruction, these results do not directly address what many consider the most serious urinary problem caused by brachytherapy, the risk of long-term urinary incontinence, the presumed consequence of acute urethral necrosis, described by Blasko and colleagues in the pioneering Seattle brachytherapy group (27). However, as we have argued elsewhere, since the magnitude or these urinary symptoms is primarily determined by the same cause, the intensity and extent of urethral radiation, it is reasonable to consider short-term urinary symptoms, especially when parallel results parallel results are found using 2 distinct, validated measures of urinary function (42).

Other results are less consistent with our earlier report. We found little evidence that MBT patients experience greater treatment-induced bowel problems compared to USBT patients nor that they experience less sexual dysfunction, as we had reported earlier (42). The latter result was

disconcerting, because of the better pretreatment sexual function of the MBT patient group, a possible indicator or lesser vulnerability to treatment-induced dysfunction. However, the potential for confounding implied in noting the better MBT patients' baseline sexual function suggests an alternate explanation for the earlier observation. While the MBT patient group at baseline gave evidence of self-selection that might lead to better functional outcomes, those differences were much greater in the earlier study population (42). Therefore, the earlier observation may have simply reflected confounding by treatment indication, as we noted in the earlier report.

Finally, however, to our surprise, we found differences of comparable magnitude *between* USBT subgroups in the mean increases in both urinary dysfunction scales, suggesting that factors other than the MBT technique's planned reduction in periurethral radiation can produce substantial differences in short-term treatment-related urinary symptoms, as well as in the bowel problems and sexual dysfunction scales. This entirely unexpected result is on one hand unsurprising, since it implies that a medical technology differs in its results depending on the treatment team and other unspecified factors. Given the complexity of prostate brachytherapy, such variability should be even more expected. The variability in functional outcomes between USBT groups obscured differences between MBT and USBT by increasing variability in the outcome measures. However, it provides an additional line of investigation, which we plan to pursue, examining factors which may be associated with variations in patients outcomes within USBT patient subgroups.

Summary. Our initial comparison of functional outcomes provides support for both our earlier observations and the guiding assumption that motivated the development of the MBT technique, the belief that avoiding urethral irradiation can importantly ablate acute treatment-related urinary symptoms, and provides hope that such changes can attenuate long-term urinary incontinence, due to acute urethral necrosis, a likely related and perhaps more serious treatment-related quality of life problem. We found less support for our earlier observations that MBT increases treatment-related bowel dysfunction or decreases treatment-related sexual dysfunction, although these results suggest that confounding may have accounted for the earlier observations, as we suggested. Finally, the substantial differences in outcomes between USBT subgroups raise the possibility of identifying important additional factors that may increase of attenuate the treatment-related complications of brachytherapy.

Abbreviations

CT	computed tomography
CTV	clinical target volume
DVH	dose volume histogram
MR	magnetic resonance
MRI	magnetic resonance imaging
MBT	magnetic resonance image guided prostate brachytherapy
MRI	magnetic resonance imaging
PSA	prostate-specific antigen
XRT	radiation therapy
PR	radical prostatectomy

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TABLES

Table 1. Sociodemographic and clinical characteristics of 267 patients with early prostate cancer who underwent brachytherapy and completed 3-month follow-up in the study

Characteristic	Level	MRI-guided BT	All U/S-guided BT	U/S-guided BT (1)	U/S-guided BT (2)	P-value
Number of Patients		75	201	116	85	
Age	Median	64	68	69	67	0.002†
	Mean	64.2	67.1	68.1	65.8	0.02#
	Range	47-80	49-81	51-81	49-79	
Race	Caucasian	66 (94%)	181 (95%)	101 (93%)	80 (96%)	0.86†
	African-American	4 (6%)	8 (4%)	6 (6%)	2 (3%)	0.74#
	Asian	0 (0%)	2 (1%)	1 (1%)	1 (1%)	
	Unknown (n)	5	10	8	2	
Currently married	%	52 (74%)	150 (77%)	84 (76%)	66 (80%)	0.62†
	Unknown (n)	5	7	5	2	0.60#
Highest Education	High School or Less	7 (10%)	44 (23%)	26 (24%)	18 (22%)	0.0002†
	Some College to Some Grad School	25 (36%)	91 (48%)	52 (47%)	39 (48%)	0.89#
	Grad/Professional Degree	37 (54%)	56 (29%)	32 (29%)	24 (30%)	
	Unknown (n)	6	10	6	4	
Physical Component Summary of SF-12*	Median	56	56	56	55	
	Mean	53.6	52.6	52.9	52.1	0.34†
	Range	32.8-63.7	22.8-65.4	22.8-65.4	23.3-63.8	0.50#
Mental Component Summary of SF-12*	Median	56	56	56	56	
	Mean	52.9	53.6	53.3	53.9	0.53†
	Range	30.5-61.5	27.1-64.1	27.5-64.1	27.1-63.9	0.66#
Index of Co-Existent Disease (ICED)	0	15 (31%)	43 (31%)	30 (31%)	13 (33%)	1.00†
	1	33 (67%)	89 (65%)	63 (65%)	26 (65%)	0.81#
	2 or 3	1 (2%)	5 (4%)	4 (4%)	1 (2%)	
	Unknown (n)	26	64	19	45	
Pretreatment Prostate-Specific Antigen (PSA)	Median (ng/dl)	5	5	5	5	0.38†
	Mean (ng/dl)	5.2	5.5	5.4	5.8	0.34#
	Range (ng/dl)	1.3-10.1	0.6-14.0	0.6-14.0	1.6-12.0	
	≤ 10 ng/dl	48 (98%)	130 (95%)	92 (95%)	38 (95%)	
	10 – 20 ng/dl	1 (2%)	7 (5%)	5 (5%)	5 (5%)	
	> 20 ng/dl					
	Unknown (n)	26	64	19	45	

Gleason Score	4 – 6	43 (88%)	108 (79%)	79 (82%)	29 (73%)	0.22†
	7	6 (12%)	27 (20%)	16 (17%)	11 (27%)	0.25#
	8 – 10	0 (0%)	1 (1%)	1 (1%)	0 (0%)	
	Unknown (n)	26	65	20	45	
Clinical Stage	T_1	46 (98%)	123 (93%)	87 (93.6%)	36 (92.3%)	0.46†
	T_2	1 (2%)	9 (7%)	6 (6.4%)	3 (7.7%)	0.72#
	Unknown (n)	28	69	23	46	
Risk Category	Low (%)	40 (85%)	98 (75%)	71 (77%)	27 (70%)	0.15†
	Intermediate (%)	7 (15%)	32 (24%)	20 (22%)	12 (30%)	0.38#
	High (%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)	
	Unknown (n)	28	70	24	46	

*Medical Outcomes Study Short-form Health Survey

†MRI-guided vs. Ultrasound-Guided #p-values are for us-1 vs us-2

Table 2. Time course and changes of unadjusted urinary, bowel and sexual function scales for 267 patients with early prostate cancer who underwent brachytherapy and completed 3-month follow-up in the study.

	Time of survey				
Scale	Baseline Score (SD)	3 Months Score (SD)	BL->3 mo Change	24 Months Score (SD)	BL->24 mo Change
Urinary obstruction/irritation					
Ultrasound-guided Brachytherapy	17.9 (11.2)	41.3 (20.5)	23.8	26.9 (16.2)	8.4
Hospital 1 ($USBT_1$)	17.3 (10.5)	36.4 (18.5)	19.7	24.9 (14.8)	7.5
Hospital 2 ($USBT_2$)	18.8 (12.1)	48.6 (21.3)	29.4	29.3 (17.8)	9.7
MRI-guided Brachytherapy (MBT)	21.8 (12.8)	33.3 (16.6)	9.3	27.1 (11.9)	0.3
All patients	19.0 (11.8)	39.1 (19.8)	20.1	26.9 (15.2)	6.5
Urinary incontinence					
Ultrasound-guided Brachytherapy	3.4 (9.7)	12.1 (18.7)	8.7	11.1 (16.2)	7.0
Hospital 1 ($USBT_1$)	3.9 (11.2)	9.7 (18.0)	5.6	10.7 (14.4)	6.3
Hospital 2 ($USBT_2$)	2.7 (7.1)	15.6 (19.2)	13.1	11.5 (18.3)	7.7
MRI-guided Brachytherapy (MBT)	4.1 (10.3)	7.1 (16.1)	2.6	4.4 (9.6)	-1.3
All patients	3.5 (9.8)	10.9 (18.2)	7.2	9.6 (15.2)	5.1
Bowel problems					
Ultrasound-guided Brachytherapy	4.1 (7.2)	9.2 (11.0)	5.2	7.2 (11.2)	3.5
Hospital 1 ($USBT_1$)	3.7 (6.1)	7.7 (10.1)	3.9	6.0 (11.1)	2.5
Hospital 2 ($USBT_2$)	4.6 (8.3)	11.2 (11.9)	7.0	8.6 (11.4)	4.8
MRI-guided Brachytherapy (MBT)	3.7 (5.4)	9.8 (11.6)	5.8	9.6 (10.4)	4.2
All patients	4.0 (6.7)	9.3 (11.2)	5.4	7.7 (11.0)	3.7
Sexual dysfunction					
Ultrasound-guided Brachytherapy	52.0 (29.5)	53.5 (29.1)	1.5	59.7 (31.4)	9.5
Hospital 1 ($USBT_1$)	56.8 (29.9)	57.1 (29.6)	1.2	59.6 (30.8)	5.2
Hospital 2 ($USBT_2$)	45.6 (27.8)	48.7 (27.8)	1.9	59.8 (32.8)	15.3
MRI-guided Brachytherapy (MBT)	39.9 (21.9)	45.1 (25.1)	6.4	52.2 (33.2)	12.6
All patients	48.6 (28.1)	51.5 (28.3)	2.8	58.2 (31.7)	10.2